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Assessment of Bidirectional Relationships Between Physical Ac and Depression Among Adults

A 2-Sample Mendelian Randomization Study

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Key Points

Question

Does physical activity have a potential causal role in reducing risk for depression?

Findings

In this 2-sample mendelian randomization study using genetic instruments from large-scale genom
association studies to support potential causal inference, higher levels of physical activity (indexec
objective accelerometer data) were linked to reduced odds for major depression.

Meaning

Findings strengthen empirical support for physical activity as an effective prevention strategy for depression.

Abstract

Importance

Increasing evidence shows that physical activity is associated with reduced risk for depression, po
a potential modifiable target for prevention. However, the causality and direction of this associatio
clear; physical activity may protect against depression, and/or depression may result in decreased
activity.

Objective

To examine bidirectional relationships between physical activity and depression using a geneticall
informed method for assessing potential causal inference.

Design, Setting, and Participants

This 2-sample mendelian randomization (MR) used independent top genetic variants associated w
physical activity phenotypes—self-reported (n = 377 234) and objective accelerometer-based (n =
084)—and with major depressive disorder (MDD) (n = 143 265) as genetic instruments from the la
available, nonoverlapping genome-wide association studies (GWAS). GWAS were previously con
in diverse observational cohorts, including the UK Biobank (for physical activity) and participatin
in the Psychiatric Genomics Consortium (for MDD) among adults of European ancestry. Mendelia
randomization estimates from each genetic instrument were combined using inverse variance weig
meta-analysis, with alternate methods (eg, weighted median, MR Egger, MR–Pleiotropy Residual
and Outlier [PRESSO]) and multiple sensitivity analyses to assess horizontal pleiotropy and remov
outliers. Data were analyzed from May 10 through July 31, 2018.

Main Outcomes and Measures

MDD and physical activity.

Results

GWAS summary data were available for a combined sample size of 611 583 adult participants. Me
randomization evidence suggested a protective relationship between accelerometer-based activity
MDD (odds ratio [OR], 0.74 for MDD per 1-SD increase in mean acceleration; 95% CI, 0.59-0.92
.006). In contrast, there was no statistically significant relationship between MDD and accelerome
based activity ($\beta = -0.08$ in mean acceleration per MDD vs control status; 95% CI, -0.47 to 0.32;
Furthermore, there was no significant relationship between self-reported activity and MDD (OR, 1
MDD per 1-SD increase in metabolic-equivalent minutes of reported moderate-to-vigorous activit
CI, 0.57-3.37; $P = .48$), or between MDD and self-reported activity ($\beta = 0.02$ per MDD in standard
metabolic-equivalent minutes of reported moderate-to-vigorous activity per MDD vs control statu
CI, -0.008 to 0.05; $P = .15$).

Conclusions and Relevance

Using genetic instruments identified from large-scale GWAS, robust evidence supports a protectiv

relationship between objectively assessed—but not self-reported—physical activity and the risk fo
Findings point to the importance of objective measurement of physical activity in epidemiologic s
mental health and support the hypothesis that enhancing physical activity may be an effective prev
strategy for depression.

Introduction

Depression is a common psychiatric condition that represents a leading cause of disability worldw
Despite this, efforts to prevent depression have been challenging, with few established protective 1
particularly modifiable targets for prevention. One promising target is physical activity, defined br
musculoskeletal movement resulting in energy expenditure.[2] The relationship between physical ac
and depression has received much attention in recent years. For example, meta-analytic data from
randomized clinical trials[3] have suggested that physical activity is linked to reduced depressive sy
in at-risk populations, and prospective studies[4,5] have demonstrated associations between higher l
physical activity and decreased risk for later depression.

Although such findings point to a potential protective role of physical activity for depression, seve
questions remain. First, does physical activity causally influence risk for depression—or is this bet
explained by reverse causation? Some studies[6,7] show that depression may also lead to reduced ph
activity, but few studies have simultaneously tested both directional relationships. Second, does
measurement of physical activity matter? Literature to date has relied mostly on self-reported mea
activity,[5] which may be subject to confounding by participant mood, memory inaccuracy, and soci
desirability bias.[8] Third, does the relationship between physical activity and depression persist wh
potential confounding is minimized? Although randomized clinical trials minimize confounding fi
unaccounted variables by design, they are intensive to conduct and have been of relatively limited
with a mean of fewer than 60 participants per trial.[3,9,10] More critically, randomized clinical trials
focused on treating symptoms in depressed individuals rather than testing preventive effects of ph
activity on depression, which has population-wide implications but requires large samples unselec
depression. The most convincing evidence to date that physical activity is associated with a reduce
for depression comes from meta-analyses of prospective studies,[5] which are high quality yet still l
by the breadth of behavioral, social, and genetic confounders that cannot be fully ruled out in obse
designs.

Mendelian randomization (MR) is an alternative method for potential causal inference that treats g
variation as a natural experiment in which individuals are essentially assigned to higher vs lower r
levels of a nongenetic exposure during their lifetime.[11] Because genetic variants are considered to
allocated randomly before birth, they are relatively independent of environmental factors and estal
well before onset of disease, thereby minimizing issues of residual confounding and reverse causa
limit typical observational studies. If an exposure such as physical activity causally influences an c
such as depression, then a variant that affects physical activity should be expected to influence dep
to a proportional degree, provided no separate pathway exists by which this variant can affect dep
phenomenon known as *horizontal pleiotropy*. Under these conditions, variants strongly associated
exposure of interest may serve as proxies, or instruments, for estimating potential causal relationsl
an outcome (Figure 1). In a 2-sample MR design, instruments can be extracted from summary stat
large-scale, nonoverlapping genome-wide association studies (GWAS), which have recently becor
available for physical activity[12] and major depressive disorder (MDD).[13] Herein, we apply bidirec
MR to assess the potential causal relationship of physical activity with the risk for depression, and

versa. Furthermore, we examine genetic instruments for physical activity assessed subjectively via report and objectively using wearable accelerometers.

Methods

This study relied on deidentified summary-level data that have been made publically available; eth approval had been obtained in all original studies. Summary data were available for a combined sa 611 583 adult participants, with corresponding GWAS sample sizes detailed below. Data were ana this study from May 10 through July 31, 2018.

Data Sources and Instruments

Physical Activity We drew on summary statistics from a recent GWAS of physical activity condu among UK Biobank Study participants.[12] This GWAS examined the following 2 continuous physi activity phenotypes: (1) self-reported moderate-to-vigorous physical activity (in standardized units inverse-normalized metabolic-equivalent minutes per week) and (2) objective accelerometer-based activity, specifically overall mean acceleration (in milligravities across at least 72 hours of wrist-w accelerometer wear). The GWAS for self-reported activity (n = 377 234) identified 9 independent wide significant single-nucleotide polymorphisms (SNPs), although SNP-based heritability was m approximately 5%.[12] The GWAS for accelerometer-based activity (n = 91 084) identified only 2 independent genome-wide significant SNPs, although SNP-based heritability was estimated much at 14%. These heritability estimates suggest that SNPs beyond those currently identified as genom significant may contribute to variation in physical activity. Given this, we used the following 2 set genetic instruments: (1) only SNPs previously reported as genome-wide significant and (2) top SN meeting a more relaxed threshold ($P < 1 \times 10^{-7}$). This method of relaxing the statistical threshold genetic instruments has been used in psychiatric MR research when few significant SNPs are available.[14,15] When the more relaxed threshold was used, we clumped SNPs for independence (i SNPs were correlated at $r^2 > 0.001$, only 1 representative SNP was retained) based on European an reference data from the 1000 Genomes Project. Where SNPs for the exposure phenotype were not available in the summary statistics of the outcome phenotype, we replaced them with overlapping SNPs in high-linkage disequilibrium ($r^2 > 0.80$) identified using the LDproxy search on the online platform LDlink (https://ldlink.nci.nih.gov/). Resulting lists of instrument SNPs for each phenotyp given in eTables 1 to 4 in the Supplement.

Depression We drew on summary statistics from the largest and most recent GWAS for MDD, de a lifetime diagnosis of major depression based primarily on structured assessments by trained inter clinician-administered checklists, or medical record review.[13] Overall, this case-control GWAS ide 44 independent genome-wide significant SNPs for MDD. For the MR analysis, we used meta-anal results for MDD that left out UK Biobank samples, because the physical activity GWAS was also conducted in the UK Biobank, and without 23andMe samples owing to general access constraints. elimination resulted in a GWAS meta-analytic subsample of 143 265. As instruments, we used ind clumped SNPs meeting a relaxed threshold ($P < 1 \times 10^{-6}$) to account for the reduced meta-analytic subsample, with similar procedures for identifying proxy SNPs as needed. The resulting list of ins SNPs is found in eTable 5 in the Supplement.

Statistical Analysis

Mendelian randomization analyses were conducted in the R computing environment using the

TwoSampleMR package (R Project for Statistical Computing). This package harmonizes exposure outcome data sets containing information on SNPs, alleles, effect sizes (odds ratios [ORs] convert statistics by log transformation), standard errors, *P* values, and effect allele frequencies for selecte exposure instruments. Herein, we allowed the forward strand of ambiguous SNPs to be inferred w possible based on allele frequency information; however, strand-ambiguous SNPs with intermedia allele frequencies (>0.42) were considered unresolvable. We also conducted sensitivity analyses w strand-ambiguous SNPs were excluded from MR analysis, which did not change the pattern of fine thus, results using the full set of SNPs were reported.

For each direction of potential influence, we combined MR estimates using inverse variance–weig (IVW) meta-analysis, which essentially translates to a weighted regression of SNP-outcome effect SNP-exposure effects where the intercept is constrained to zero. Again, results can be biased if ins SNPs show horizontal pleiotropy, influencing the outcome through causal pathways other than the exposure, thereby violating instrumental variable assumptions.[16] We therefore compared IVW res other established MR methods whose estimates are known to be relatively robust to horizontal ple although at the cost of reduced statistical power.[17] These methods include the weighted median ap which selects the median MR estimate as the causal estimate,[18] and MR Egger regression, which a the intercept to be freely estimated as an indicator of average pleiotropic bias.[16] We also applied N PRESSO (Pleiotropy Residual Sum and Outlier)[19] to detect and correct for any outliers reflecting pleiotropic biases for all reported results. Effect estimates are reported in β values where the outco continuous (ie, self-reported or objectively assessed physical activity levels) and converted to ORs the outcome was dichotomous (ie, MDD status).

To assess robustness of significant results, we conducted further tests for horizontal pleiotropy usi analytic methods to detect heterogeneous outcomes, including leave-1-SNP-out analyses, the mod Cochran Q statistic, and the MR Egger intercept test of deviation from the null.[20] These tests vary assumptions but essentially capture the extent to which the effect for 1 or more instrument SNP is exaggerated in magnitude, as would be the case if that SNP not only acted through the hypothesize pathway, but through other unaccounted causal pathways. Finally, we looked up each instrument S their proxies ($r^2 > 0.80$) in the PhenoScanner GWAS database (version 2; http://phenoscanner.medschl.cam.ac.uk) to assess any previous associations ($P < 1 \times 10^{-5}$) with po confounding traits and assessed the effects of manually removing these SNPs from the MR analys out possible pleiotropic effects.

Results

Accelerometer-Based Physical Activity and Depression

We found evidence of a protective causal relationship between accelerometer-based physical activ MDD (IVW OR, 0.74 for MDD per 1-SD unit increase in mean acceleration; 95% CI, 0.59-0.92; *l* .006); weighted median and MR Egger analysis yielded similar pattern of effects (Table 1), with 1 meeting the relaxed statistical threshold (Figure 2). The MR estimate was not statistically significa only 2 genome-wide significant SNPs (IVW OR, 1.12; 95% CI, 0.72-1.75; *P* = .60) (eTable 6 and 1 in the Supplement), which provided insufficient data for alternative MR methods and sensitivity analyses. For the 10 SNPs, MR-PRESSO did not detect any potential outliers. Furthermore, analys leaving out each SNP revealed that no single SNP drove these results but rather reflected an overa combined pattern of opposite relationships with physical activity vs MDD (eFigure 2 in the Suppl Similarly, the modified Q statistic indicated no notable heterogeneity (Q = 6.01; *P* = .74) across ins

SNP effects. The MR Egger intercept test further suggested no horizontal pleiotropy (intercept, 0.0
standard error, 0.02; $P = .60$). In the PhenoScanner database, we identified 2 of the 10 SNPs for
accelerometer-based activity nominally associated with depression-relevant traits (ie, rs59499656
body mass index and rs9293503 with educational attainment). However, removing both SNPs did
change the pattern of results. When we further mapped SNPs to known genes in public databases a
examined whether any genes have been implicated in GWAS of relevant traits, removing SNPs pro
no substantive change in results (eMethods 1, which includes eFigure 3 and eTables 6 and 7, in the
Supplement).

In the other direction, across all MR methods, we found no evidence of causal relationships of ME
accelerometer-based activity (Table 2). MR-PRESSO detected 1 outlier, and MR estimates remain
after removal of this outlier (IVW $\beta = -0.08$ in mean acceleration per MDD vs control status; 95%
-0.47 to 0.32; $P = .70$). The weighted median and MR Egger yielded a similar pattern of effects (T
and Figure 3).

Self-reported Physical Activity and Depression

In contrast, we found no statistically significant evidence of a relationship between self-reported a
and MDD, regardless of instrument SNP threshold (outlier-adjusted IVW OR, 1.28 for MDD per 1
increase in metabolic-equivalent minutes of moderate-to-vigorous activity [95% CI, 0.87-1.90; $P =
24 top SNPs; IVW OR, 1.45 for MDD per 1-SD increase in metabolic-equivalent minutes of mode
vigorous activity [95% CI, 0.57-3.37; $P = .48$] for 6 genome-wide significant SNPs) (eTables 9-11
eFigures 4 and 5 in the Supplement), or between MDD and self-reported activity (for 14 top SNPs
adjusted IVW $\beta = 0.02$ in standardized metabolic-equivalent minutes of moderate-to-vigorous acti
MDD vs control status; 95% CI, -0.008 to 0.05; $P = .15$) (eTable 12 and eFigure 6 in the Supplem

Discussion

Depression is a common and debilitating condition, with a high societal burden of morbidity and
mortality.[21] As such, identification of effective strategies for preventing depression has substantial
implications for improving population health. Recent evidence has suggested that physical activity
protect against the risk for depression.[3,4,5] However, if the relationship between physical activity a
depression is not causal, recommendations to promote physical activity, while beneficial for other
outcomes, would yield limited results for depression. To strengthen causal inference, we apply a
genetically informed method. Using MR with genetic instruments selected from large-scale GWAS
find evidence supporting a potential causal relationship between physical activity and a reduced ri
depression.

Our results extend current literature in a number of ways. First, we examined self-reported and obj
measured (ie, accelerometer-based) physical activity and discovered that findings on the relationsh
depression are specific to objectively measured—but not self-reported—activity. Meta-analytic da
shown that self-report and objective measures can yield discrepant estimates of physical activity.[8,]
Self-report measures of activity may be affected by mood states and cognitive biases that also affe
mental health, making it difficult to ascertain whether observed associations are true or simply arti
a common liability. For example, individuals vulnerable to depression may perceive themselves as
inactive and disengaged than their peers or compensate by overreporting activity. Although this do
invalidate the utility of self-reported measures, verifying their conclusions with objective measure
essential. Prior work has indicated that objectively measured physical activity is more heritable[12]

hence may be closer to biological processes that could directly affect depression, as well as more powerfully instrumented by SNPs in the MR context.[24] Only 1 prior study,[25] to our knowledge, ha incorporated genetic information, using a twin-based design, to assess the relationship between ph activity and depression. Contrary to our study, it did not yield evidence of such a relationship, perh owing to self-report measures and restricted definition of physical activity as leisure exercise (ie, intentionally performed to improve or maintain fitness) vs physical activity more broadly.[2]

We estimated a moderate but significant reduction of MDD risk per 1-SD increase in objectively n physical activity. One SD of objectively measured physical activity in the UK Biobank Study has l reported to be approximately 8 milligravities (or 0.08 m/s^2) of acceleration in a mean 5-second wi analyzed accelerometer data.[12,26] Although no straightforward translation of these values into ene expenditure or step-based metrics is available, an 8-milligravity increase in mean acceleration is ro what we might observe in a 24-hour period if—for example—a person replaced sedentary behavio 15 minutes of vigorous activity (eg, running); just more than 1 hour of moderate physical activity walking); or some combination of light activity (eg, standing, stretching, easy chores) and more vi activity (eFigure 7 and eTable 13 in the Supplement).

Second, it has remained unclear to date whether inverse associations between physical activity an depression are owing potentially to a protective relationship between physical activity and depress and/or a relationship between depression and reduced physical activity. Using bidirectional MR, w evidence of only 1 direction of this relationship, where physical activity demonstrated a potential relationship with depression, while depression does not appear to have a such a relationship with p activity. Other factors may better explain the observed depression-activity relationship[7] rather than depression directly compromising physical activity. For example, underlying conditions such as cl pain could interfere with activity and lead to depression. However, our MR analyses may not be cu powered to detect small effects (for calculations, see eMethods 2 in the Supplement) that may bec apparent when future discovery GWAS are expanded.

Limitations

This study has several limitations. First, although we drew on the largest available GWAS, some id few genome-wide significant SNPs, which could result in relatively weak genetic instruments. To this, we applied statistical criteria to include additional SNPs as instruments. This approach has be in other MR studies where currently known genome-wide significant SNPs are limited.[14,15] Secor despite selecting strongly associated SNPs, common SNPs do not yet explain much total variance complex traits[27] and so cannot be considered exact proxies of the exposure. In addition, because w yet know the biological action of these SNPs, it is impossible to fully rule out pleiotropic mechani without detailed functional follow-up of these loci, although we conducted the most up-to-date arr sensitivity analyses to rule out horizontal pleiotropy. Although horizontal pleiotropy is a concern f inference, vertical pleiotropy—in which an exposure acts on an outcome via other variables along same causal pathway—is acceptable.[17] For example, if physical activity causally reduces body ma index, and then body mass index causally affects MDD, this represents vertical pleiotropy for whic should not unnecessarily penalize the MR estimate.[24] However, it is reassuring that our observed l estimate was robust across sensitivity analyses, suggesting negligible bias from evident sources of pleiotropy. Third, we used summary GWAS data for MDD and not for depressive symptoms in inc with or without MDD. Although meta-analyses have shown that physical activity is associated wit improved symptoms in individuals with depression,[9,10,28] our study was not designed to address t

Also, we only considered overall levels of physical activity in relation to depression, whereas rece
has revealed complicated associations between the type, duration, frequency, and intensity of phys
activity and mental health[29] that could affect the size and direction of observed MR estimates but
not be assessed in the present study. Fourth, SNPs associated with physical activity were identified
UK Biobank Study, which consists of individuals aged 40 to 70 years, whereas samples in the MD
GWAS included a wider range of age groups. Physical activity in younger individuals may be influ
by other variants that share different associations with MDD, although such GWAS data are not ye
available. Moreover, we do not have demographic data on all of the GWAS participants, such as a
sex, which limits clinical generalizability of these findings to other populations. Finally, we canno
interpret effect sizes in the same way as a clinical trial in which individuals are assigned to a discr
program of physical activity of defined length, because MR estimates reflect lifelong effects of ass
to genetic variants. However, our MR estimate is notably similar in magnitude to those of recent n
analytic observational data.[5]

Despite these limitations, our application of MR represents a test of whether genetic instruments p
independent support for potentially protective relationships between physical activity and depressi
Our novel triangulation of genetic variants as instruments for causal inference[30] obviates typical
challenges for observational research while strengthening evidence from such studies.[3,4,5] Stronge
evidence of causal relationships is of great importance because few modifiable factors for preventi
depression are known. If physical activity truly reduces risk for depression, it would be useful to p
physical activity not only in the population at large, where this can yield public health returns at th
of human productivity and reduced health care burden, but also for individuals at risk for developi
depression, such as adolescents or those facing depressogenic exposures, such as violence-expose
individuals or workers in high-stress environments.

Conclusions

This study leverages MR to support causal inference regarding putative protective factors in menta
Our findings validate a potential protective relationship between physical activity and depression a
to the importance of objective measurement of physical activity in epidemiologic studies of menta
Overall, this study supports the hypothesis that enhancing physical activity is an effective preventi
strategy for depression.

Notes

Supplement.

eTable 1. Top SNPs (n = 10) for Accelerometer-Based Activity ($P < 1 \times 10^{-7}$)

eTable 2. Genome-Wide Reported SNPs (n = 2) for Accelerometer-Based Activity

eTable 3. Top SNPs (n = 25) for Self-Reported Activity ($P < 1 \times 10^{-7}$)

eTable 4. Genome-Wide Reported SNPs (n = 8) for Self-Reported Physical Activity

eTable 5. Top SNPs (n = 17) for Depression ($P < 1 \times 10^{-6}$)

eTable 6. Mendelian Randomization Results of Accelerometer-Based Activity (Genome-Wide
SNPs Only) → Depression

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Figures and Tables

Figure 1.
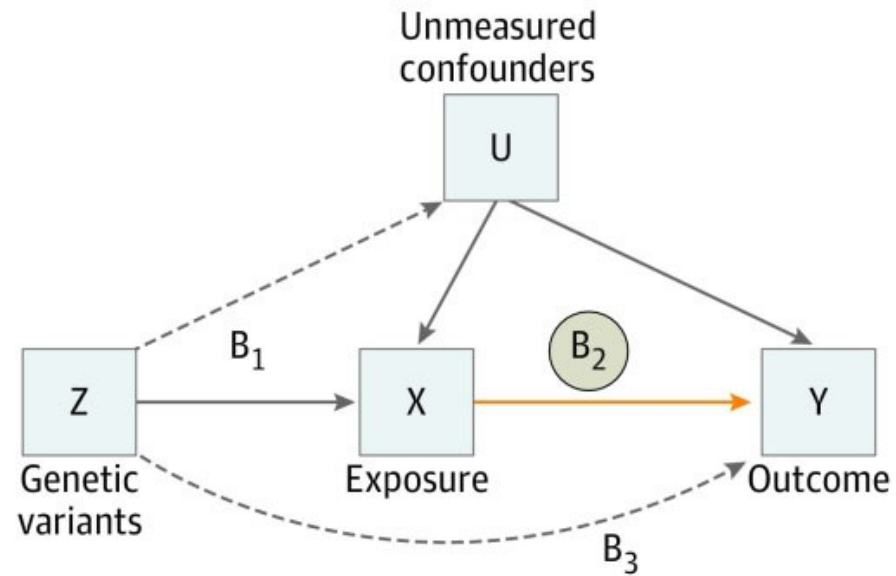
Mendelian Randomization (MR) Model

B_2 indicates the causal relationship of interest to be estimated, where $B_2 = B_1/B_3$. B_1 and B_3 represent estimated effects of a genetic variant on the exposure (eg, physical activity) and outcome (eg, depression), respectively. So are theorized to exist; dashed paths are theorized to be nonsignificant according to MR assumptions.

Table 1.

### MR Results for the Relationship Between Accelerometer-Based Activity Effect and MDD

Method	OR (95% CI)[a]	P Value	No. of SNPs
IVW[b]	0.74 (0.59-0.92)	.006	10
Weighted median[b]	0.71 (0.53-0.95)	.02	10
MR Egger[b]	0.57 (0.22-1.48)	.28	10

Abbreviations: IVW, inverse variance–weighted; MDD, major depressive disorder; MR, mendelian randomizati OR, odds ratio; SNP, single-nucleotide polymorphism.

[a]Indicates odds for MDD per 1-SD increase in mean acceleration.
[b]No MR-PRESSO (Pleiotropy Residual Sum and Outlier) outliers were detected. $P < 1 \times 10^{-7}$ for top SNPs.

Figure 2.
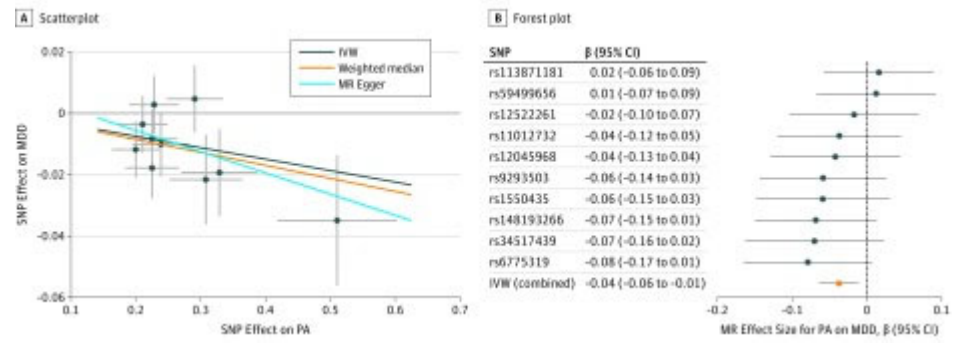
Mendelian Randomization (MR) Plots for Relationship of Accelerometer-Based Activity With Major Dep Disorder (MDD)

A, Scatterplot of single-nucleotide polymorphism (SNP) potential effects on physical activity (PA) vs MDD, wit slope of each line corresponding to estimated MR effect per method. B, Forest plot of individual and combined S estimated effects sizes. Data are expressed as raw β values with 95% CI. $P < 1 \times 10^{-7}$ for top SNPs. IVW indica inverse variance–weighted method.

Table 2.

### MR Results for the Relationship Between MDD and Accelerometer-Based Activity

Method	β (95% CI)[a]	P Value	SNPs
Main model[b]			
IVW	−0.08 (−0.47 to 0.32)	.70	15
Weighted median	−0.07 (−0.62 to 0.48)	.82	15
MR Egger	−0.13 (−2.11 to 1.86)	.90	15
With outlier			
IVW	0.05 (−0.41 to 0.51)	.83	16
Weighted median	−0.04 (−0.59 to 0.51)	.98	16
MR Egger	1.05 (−0.96 to 3.06)	.33	16

Abbreviations: IVW, inverse variance–weighted; MDD, major depressive disorder; MR, mendelian randomizati OR, odds ratio; SNP, single-nucleotide polymorphism.

[a]Indicates change in mean acceleration per MDD vs control status.
[b]Indicates model with MR-PRESSO (Pleiotropy Residual Sum and Outlier) outlier (rs78676209) removed. $P <$ $10^{−6}$ for top SNPs.

Figure 3.
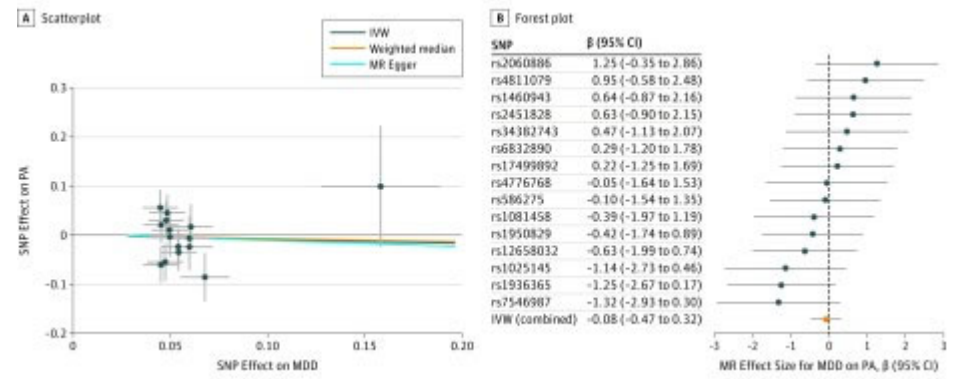
**Mendelian Randomization (MR) Plots for Relationship of Major Depressive Disorder (MDD) With Accele
Based Activity**

A, Scatterplot of single-nucleotide polymorphism (SNP) effects on MDD vs their effects on physical activity (PA
slope of each line corresponding to estimated MR effect per method. B, Forest plot of individual and combined S
estimated effects sizes. Data are expressed as raw β values with 95% CI. IVW indicates inverse variance–weight
method.